REMARKS

Claims 1-3 are pending in this application. Reconsideration in view of the foregoing amendments and following remarks is respectfully requested. Further in response to the Restriction Requirement, Claims 5-8 are canceled subject to Applicants' reservation of the right to file a divisional application to the subject matter thereof at the appropriate time.

The rejection of Claims 1-3 under the first paragraph of 35 U.S.C. §112 is obviated by the amendment of Claim 1 to limit the scope of the claimed method to the detection of Alzheimer's Disease. In addition, Claim 1 is amended to recite that, in the claimed method, a reduction in the level of binding of the proteins to the labeled wheat germ agglutinin is indicative of Alzheimer's Disease in the patient. In order to provide antecedent basis for "the patient" in step (e), it is recited that the claimed method is to the detection of Alzheimer's Disease "in a patient" and, in step (a), the body fluid to be tested is obtained "from the patient". "Protein" in steps (b) and (c) is made plural to provide antecedent basis for the plural in step (e). Support for the amendment to Claim 1 is found in Claim 4, which is canceled, and in the present specification, for example, in Figures 1 -3 and the detailed description thereof appearing on pages 3 and 4. Withdrawal of the rejection is respectfully requested.

The rejection of Claims 1-4, now Claims 1-3, under 35 U.S.C. §103 as being unpatentable over Saez-Valero *et al.* in view of Sigma Chemical Catalog and Savage *et al.* is respectfully traversed. Saez-Valero *et al.* is representative of detection methodology for Alzheimer's Disease (AD) prior to the present invention and fundamentally differs from the claimed method. In the prior work by the present inventors and others including Saez-Valero *et al.*, it was found that the binding of certain biomarkers, such as acetyl cholinesterase (AChE) and butylcholinesterase (BuChE), to wheat germ agglutinin (WGA) is increased in AD patients. In contrast, the present method is founded on the

discovery that there is an overall reduction in total protein binding to WGA in AD patients.

It is clearly evident from the foregoing that the previous work by Saez-Valero *et al.* and others, based on the observation that binding of WGA to both AChE and BuChE is increased in patients with AD, would not suggest the present method to one of ordinary skill in the art because such teachings are premised of observing an increase in binding, whereas the present method is based on the discovery that, in AZ patients, there is a decrease in binding of proteins to WGA. Therefore, whether or not Saez-Valero *et al.* teach the use of labeled WGA is respectfully submitted to be irrelevant to the question of would their teaching render the claimed method obvious to one of ordinary skill in the art. Likewise, the teaching of Savage *et al.* is not relevant because the thrust of the teaching of Saez-Valero *et al.* is the exact opposite from that of the present invention.

It is stated in the Office Action under reply that the rejection over Saez-Valero *et al.* is justified in that "comprising" in the present claims could include other method steps. While that may be arguable so, it is not relevant when such steps bear no relation to the determinant observation in the claimed method. The previous work exemplified by Saez-Valero *et al.* shows that, while not entirely specific for AD, binding of AChE and BuChE to WGA is increased in AD patients in comparison to control samples. While not wishing to be bound by any theory, it is believed that the present method is based on a general protein glycosylation defect in AD patients. As this defect affects many different proteins, it is believed that either there is a change in the synthesis of the carbohydrate, or there is a defect in the de-glycosylation (removal of certain types of sugars from the surface of the carbohydrate).

In contract to the present method, the work described in the prior art, exemplified by Saez-Valero *et al.*, has repeatedly shown that the change in AChE glycosylation is the result of the production of a single minor isoform of the enzymes.

This is probably also true for the change in BuChE glycosylation, although that has not been proved. In other words, the effect is related to a change in expression of the protein itself, not a specific change in the glycosylation step per se. Hence, it can be seen that the inclusion of a ratio calculating step or other similar determining step in the method taught by Saez-Valero *et al.* would not render the claimed method obvious to one of ordinary skill in the art because Saez-Valero *et al.* is focused on observing increases in binding, diametrically opposite from the present method. Hence, since there is nothing in Saez-Valero *et al.* or the secondary citations that would suggest to one of ordinary skill in the art that a decrease in proteins binding could be utilized to diagnose AD, it is submitted that the claims are clearly patentable thereover. Withdrawal of the rejection is respectfully requested.

The rejection of Claims 1-4, now Claims 1-3, under 35 U.S.C. §103 as being unpatentable over Small *et al.* in view of Sigma Chemical Catalog and Savage *et al.* is respectfully traversed. Like Saez-Valero *et al.*, Small *et al.* in the passage referenced in the Office Action under reply demonstrates an increase of binding of AChE to WGA. Both teach that an increase in binding of a specific biomarker is the critical criterion for their determination. However, there is neither teaching nor suggestion in either citation that measuring proteins binding to WGA and determining that a reduction in such binding would be indicative of AD. The secondary citations have been discussed above and do not render Small *et al.* any more pertinent to the claimed method, as was the case with Saez-Valero *et al.* Hence, it respectfully submitted that Claims 1-3 are patentable over Small *et al.* taken in combination with Sigma Chemical Catalog and/or Savage *et al.* Withdrawal of the rejection is in order and is respectfully requested.

The rejection of Claims 1-4, now Claims 1-3, under 35 U.S.C. §103 as being unpatentable over DeGasperi *et al.* in view of Savage *et al.* is obviated by the foregoing amendments to restrict Claim 1 to the detection of Alzheimer's Disease. It is recognized that this is so in the Office Action under reply as the rejection was not made against

Claim 4, now canceled, which is limited to AD. Since the rejection does not apply to Claims 1-3, as amended, it is respectfully requested that it be withdrawn.

The rejection of Claims 1-4, now Claims 1-3, under 35 U.S.C. §103 as being unpatentable over Szumanska *et al.* in view of Saez-Valero *et al.* is respectfully traversed. Szumanska *et al.* disclose a method for detecting changes in WGA staining in amyloid plaques using biotin labeled lectin, and show a more intense pattern exists in AD than in patients with Gersmann-Straussler syndrone, also characterized by plaques in the brain. The Examiner concludes that the method taught by Szumanska *et al.* can be used for the diagnosis of AD. This is clearly the Examiner's conclusion as it is unsupported by the citation. In fact, the authors state in the third paragraph under "Discussion" on page 8 in regard to differences in staining intensity that they may be, "...the reflection of the different time course of the formation of the plaque, age differences of patients and also of individual pathogenetic abberations". This is hardly a basis for such a conclusion.

Regardless of whether or not Szumanska *et al.* can be interpreted as providing a basis for concluding that one skilled in the art might derive a test for AD from the observations reported therein, one of ordinary skill in the art, reading it in the light of the teachings of Saez-Valero *et al.* would be inescapably drawn to investigating the techniques described therein with regard the binding characteristics of specific proteins, and focusing on characteristic <u>increases</u> in binding properties. This is clearly so because that is what Saez-Valero *et al.* focus upon. There is no teaching or suggestion in either citation that reduction of proteins binding to WGA would have any significance as a diagnostic tool for AD. It is respectfully submitted that withdrawal of the rejection is in order and such action is respectfully requested.

It is evident that the citations as a whole are focused on the use of specific tools to accomplish the solution to how to effectively diagnose AD. It is therefore considered unexpected that Applicants have found a test that is relatively straight-forward to carry

out and relies not on a specific protein, but on the binding of proteins in the sample to WGA. The present technique is economically advantageous in comparison to techniques that rely on more sophisticated apparatus to ensure that only a specific biomarker is being detected. There is nothing in the teachings of the citations, individually or in any combination, that would suggest to one of ordinary skill in the art that such a test was even feasible, given their emphasis on ever-increasing specificity.

The rejection of Claims 1-4, now Claims 1-3, under obviousness-type double patenting over Small *et al.* U.S. Patent No. 6,461,831 in view of Sigma Chemical Catalog and Savage *et al.* is respectfully traversed. It is noted that step (3) of the claimed method requires detecting the presence in a sample of AChE with an altered glycosylation pattern such that it has a relatively looser affinity for ConA and a greater affinity for WGA than AChE with an unaltered glycosylation pattern. The claimed method, therefore, is clearly based on a determination of increased binding to WGA. Such claims are clearly patentably distinct from the claims under consideration in this application and are not make more relevant thereto by the teachings of Sigma Chemical Catalog and Savage *et al.* for the reasons fully documented above. Accordingly, the rejection should be withdrawn and such action is respectfully requested.

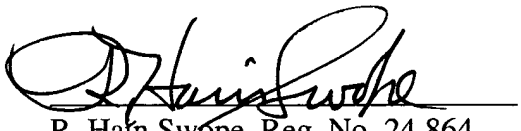
The provisional double patent rejection over Claims 28 and 29 of co-pending patent application Serial No. 10/648,548 is respectfully traversed. It is noted that Claims 28 and 29 therein have been canceled, however, the rejection will be addressed as it would apply to Claim 30, newly submitted in the most recently filed response. As with the patents discussed above, the method claimed in Serial No. 10/648,548 is directed to a determination based on an increase of a specific biomarker to WGA as being indicative of AD. While that does broadly fall under the heading of "determining the amount of a protein bound to WGA" as stated in the Office Action under reply, it is respectfully submitted that the principle of the method is diametrically opposite from the method in the present invention, the additional of non-relevant "additional steps" notwithstanding. Since the Claims under consideration are clearly patentably distinct

from those in copending application Serial No. 10/648,548, it is respectfully submitted that a double patenting rejection cannot be sustained and must be withdrawn.

Accordingly, it is respectfully submitted that Claims 1-3, as amended, clearly define patentable subject matter over the citations of record and are likewise patentably distinct from the claims of U. S. Patent No. 6,461,831 and co-pending application Serial No. 10/648,548. The above-identified application is therefore considered to be in condition for allowance and an early Notice of Allowability is courteously solicited.

Accompanying this Amendment is a Petition for a Three-Month Extension of Time thereby providing for the timely filing thereof. If there are any additional fees due in connection with the submission of this Response, the Patent & Trademark Office is authorized to charge any such fee to Deposit Account No. 03-3839. **It is <u>again</u> respectfully requested that the change in Attorney Docket No. for this application be noted and the file marked accordingly.**

Respectfully submitted,



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